Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins

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Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins

Brief title: HF With Preserved Ejection Fraction and AF

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Abstract
Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are age-related conditions that are increasing in prevalence, commonly coexist, and share clinical features. This review provides a practical update on the epidemiology, pathophysiology, diagnosis, and management of patients with concomitant HFpEF and AF. Epidemiological studies highlight the close and complex links between HFpEF and AF, the shared risk factors, the high AF occurrence in the natural history of HFpEF, and the independent contribution of each condition to poor outcomes. Diagnosis of HFpEF in the setting of AF is challenging because the symptoms overlap. AF is associated with changes in echocardiographic parameters and circulating natriuretic peptides that confound HFpEF diagnosis. Symptomatic improvement with diuretic therapy supports the presence of HFpEF in patients with concomitant AF. Important knowledge gaps need to be addressed by a multidisciplinary and translational research approach, in order to develop novel therapies that can improve prognosis.

<KW>Key words: Age; Diagnosis; Epidemiology; Natriuretic Peptides, Outcomes

Abbreviations and Acronyms
AF = atrial fibrillation
ANP = atrial natriuretic peptide
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
LA = left atrium/atrial
LV = left ventricular
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal B-type natriuretic peptide

Introduction

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are common conditions that are increasing in prevalence, and are associated with increased morbidity and mortality compared with patients without these diagnoses (1). HFpEF is as common as heart failure with reduced ejection fraction (HFrEF), and patients suffer from similar symptoms, yet lack therapeutic options with proven efficacy (2). Patients with AF are heterogeneous and share many common clinical features with patients with heart failure (HF), but demonstrate a requirement for specific management in order to improve outcomes, over and above related comorbidities (3). Both HFpEF and AF are associated with older age, hypertension, and diastolic dysfunction; therefore, these disorders are inextricably linked, both to each other and to adverse cardiovascular outcomes (1). AF is a potent and independent prognostic factor in patients with HF, increasing the risk of death in clinical trials and observational studies (4,5). The development of AF may have more of an impact in patients with HFpEF than in those with HFrEF (6,7), identifying a subgroup of patients with more advanced HFpEF and worse exercise tolerance (8). Although the combination of AF and HFpEF appears to be associated with lower mortality than AF and HFrEF, patients have similar rates of incident stroke and HF hospitalization (9). Furthermore, the severity of disease in HFpEF and HFrEF may not have been comparable in prior studies. At the very least, AF and HF require comparable attention.

Not all studies have been able to differentiate whether HFpEF or AF comes first, and there are clear diagnostic challenges in clinical practice. Identifying prevalent AF in the context of HFpEF is relatively straightforward, with well-documented electrocardiographic methods that apply to a wide range of patient populations (10). However, AF is often paroxysmal, frequently

asymptomatic, and can be easily missed (11). HFpEF remains a clinical diagnosis (12,13), combining typical symptoms and signs with echocardiographic evidence of diastolic dysfunction and "preserved" left ventricular ejection fraction (LVEF). Importantly, symptoms like dyspnea, fatigue, and impaired exercise tolerance are also the predominant symptoms of patients with AF, and largely overlap with HFpEF, making definitive diagnosis on the basis of clinical features more complex. There is ambiguity in echocardiographic diagnosis, both for the LVEF cutoff (which is a continuum), and the objective evaluation of diastolic function, which is not always easy or possible to demonstrate, particularly in the context of AF. Circulating levels of biomarkers, such as N-terminal B-type natriuretic peptides (NT-proBNPs) are also independently influenced by both conditions, making it unclear what NT-proBNP levels to use for the diagnosis of one condition in the presence of the other (2).

In this review, we aim to focus on the epidemiology, pathophysiology, diagnosis, and management of patients with concomitant HFpEF and AF. We start by summarizing available evidence regarding the prevalence and incidence of HFpEF in the setting of AF and vice versa, and then examine the underlying mechanisms by which AF begets HFpEF and HFpEF begets AF. Further, we address the diagnostic uncertainties of each condition in the presence of the other, and consider potential therapeutic strategies. Our objective is to provide clinicians with a practical guide to the key issues, and address the knowledge gaps that prevent optimal treatment of this common and high-risk group of patients.

Incidence and prevalence of HFpEF in the setting of AF

Data on the incidence and prevalence of clinical HF in patients with AF is widely available, however specific studies on HFpEF are scarce. The PREVEND (Prevention of Renal and Vascular End-Stage Disease) study is a community-based cohort in the Netherlands. Of

8,265 participants studied, 265 developed AF (total follow-up 80,352 person-years). The incidence rate of HFpEF (LVEF >50%) per 1,000 person-years was 4.90 for those with AF versus 0.85 for those without AF, a hazard ratio (HR) of 4.8 (1). AF was identified as a major risk factor for new-onset HFpEF in the Framingham Heart Study (HR: 2.5), and the presence of AF tended to predict incident HFpEF (HR: 2.3) more strongly than in HFrEF (14). Furthermore, among participants with AF, there was a higher incidence of HFpEF in women compared to men (35.1 vs. 21.2 events/1,000 person-years) (15). Surveys, registries, and trials give further insight the prevalence of HFpEF is in patients with AF, which varies between 8% and 24% (16-19), and depends on the definition (LVEF above 40% or 50%), and the type of AF (**Figure 1**). Although different definitions of HFpEF were used, it would seem prudent to suggest that HFpEF is more common in those with a longer duration of AF.

Incidence and prevalence of AF in the setting of HFpEF

Large epidemiological studies have established that HF is a potent risk factor for incident AF, with a 6-fold increase in the risk of developing AF in a previous report from the Framingham Heart Study (20). In fact, AF is the most common arrhythmia in HF, present in around one-third of patients (21,22). The prevalence of AF increases with HF severity, ranging from 5% in mild HF to 50% in severe HF (23). Specifically for HFpEF, the prevalence of AF varies between 15% and 41% (**Figure 2**).

The temporal progression of AF in HFpEF was described in 939 participants with newly diagnosed HFpEF in the Olmsted County population cohort. Two-thirds experienced AF during the course of their disease: 29% prior to diagnosis, 23% concurrent with HFpEF, and 15% after diagnosis (24). Participants with prevalent AF at the time of HFpEF diagnosis (compared to sinus rhythm) were older and had higher NT-proBNP levels and larger left atria, whereas those

with incident AF after HFpEF diagnosis had greater diastolic dysfunction. More recently, a study of the temporal associations of AF and HFpEF versus HFrEF showed that participants with HFpEF were more likely to have prevalent AF compared to HFrEF (32% vs. 23%, p = 0.002) and AF at any time (62% vs. 55%, p = 0.02) (15). In aggregate, these studies highlight the close and complex links between HFpEF and AF, the extraordinarily high occurrence of AF in the natural history of HFpEF, and the independent contribution of each condition to poor outcomes in affected patients.

Shared pathophysiology

Given that a substantial proportion of patients with HFpEF experience AF at some point during the course of their disease, shared pathophysiological mechanisms are highly likely. These may involve: 1) common risk factors and comorbidities that predispose to both conditions simultaneously; 2) mechanisms by which HFpEF gives rise to AF; and 3) mechanisms by which AF leads to HFpEF (**Figure 3**). Noncardiac comorbidities are often present in HFpEF. Pulmonary disease, diabetes mellitus, anemia, and obesity tend to be more prevalent in HFpEF patients, but renal disease and sleep-disordered breathing burdens are similar to HFrEF (25). These comorbidities are also frequently present in the setting of AF (26).

<u>Common risk factors predisposing to both HFpEF and AF simultaneously</u>

Common risk factors prominently shared between HFpEF and AF include advanced age and age-related comorbidities, such as hypertension, obesity, and sleep apnea. Vascular-ventricular stiffening, the hallmark of aging (27), plays an important role in the pathophysiology of HFpEF via left ventricular (LV) diastolic dysfunction and systolic ventricular-vascular uncoupling (28,29). Similarly, the incidence of AF increases sharply with age (30), and age-related diastolic dysfunction has been shown to contribute to AF in the general population

(31,32). Importantly, however, the incidence of AF in HFpEF exceeds that expected by aging alone (incidence rate of 69 cases/1,000 person-years in Olmsted County HFpEF (24) compared with 28.3/1,000 person-years in U.S. Medicare beneficiaries ≥65 years of age) (30).

Systemic inflammation may also link HFpEF and AF, with a new paradigm proposing HFpEF as an inflammatory disorder in which comorbidities, such as obesity, trigger widespread endothelial dysfunction, oxidative stress, and microvascular inflammation, leading to end-organ manifestations, such as diastolic dysfunction (33,34). Evidence supporting the hypothesis of endothelial microvascular inflammation in HFpEF accumulates, although definitive clinical trial data are still lacking. Histological findings in atrial biopsies support the proinflammatory milieu of HFpEF as a key mechanism underlying AF occurrence and maintenance (35). In patients undergoing AF ablation, levels of inflammatory markers, such as C-reactive protein, interleukin-6, and matrix metalloprotease-2, differed significantly between those who remained in sinus rhythm after ablation versus patients who reverted to AF (36).

Mechanisms by which HFpEF gives rise to AF

The most commonly recognized mechanism by which HFpEF gives rise to AF is via structural and functional remodeling of the left atrium (LA). LA volumes are 68% larger in HFpEF compared with age-matched controls, and 40% larger than in patients with hypertensive heart disease without HF (37). Patients with HFpEF have reduced emptying fractions and contractile reserve, compared with controls and patients with hypertension. LA enlargement in HFpEF is a well-established proarrhythmic substrate associated with atrial fibrosis (38). Abnormal distribution of gap junctions and loss of cell-to-cell coupling in areas of fibrosis contributes to electrical remodeling, increased atrial refractoriness, and development of AF (39,40). Disrupted ion-channel regulation has been demonstrated in experimental models of HF,

with reduction in the L-type calcium ion (Ca^{2+}) current, the sensitive transient outward potassium ion (K^+) current and the slow delayed rectifier K^+ current in atrial myocytes (41), whereas the transient inward sodium ion (Na^+)/Ca^{2+} exchanger current is increased (42). The increase in the Na^+/Ca^{2+} transmembrane exchange channel current gives rise to delayed afterdepolarizations, leading to arrhythmias initiated by triggered activity (43). The important role of gap junctions in atrial remodeling has also been highlighted, involving atrial connexin proteins (44) and the resultant inhomogeneity of impulse propagation, thus establishing re-entry circuits predisposing to AF. Although many of these seminal AF studies were performed in HFrEF models, the underlying concepts also apply to atrial remodeling in the setting of HFpEF.

Up-regulation of the adrenergic and renin-angiotensin-aldosterone systems have been shown in experimental models to contribute to impaired impulse propagation, atrial fibrosis, and AF in HF. Because both neuroendocrine systems are similarly up-regulated in HFpEF and in HFrEF (45), these mechanisms may underlie the development of AF in HFpEF. A further consideration includes the role of atrial natriuretic peptide (ANP), the hormone produced by the atria in response to stretch, which causes diuresis and vasodilation. Impaired natriuresis has been shown to contribute to volume overload among patients with preclinical diastolic dysfunction (46). Although normally important for homeostasis, failure of the atrium to secrete adequate amounts of ANP in HFpEF may be associated with atrial structural remodeling and mechanical dysfunction (47). Interestingly, atrial endocrine failure may be addressed by blocking neprilysin, the neutral endopeptidase that breaks down ANP.

Mechanisms by which AF gives rise to HFpEF

Because AF itself causes LA dilation, impaired atrial function, and atrial fibrosis, AF may be a direct cause of HFpEF (48). Indeed, successful cardioversion is associated with

restoration of atrial booster pump function and improved ventricular filling, with the atrial contribution to ventricular filling increasing from 30% to 47% one month after the return of sinus rhythm (49). AF is also associated with LV myocardial fibrosis (50), which, in turn, contributes to diastolic dysfunction and HFpEF (51). Furthermore, atrioventricular annular remodeling with progressive mitral and tricuspid regurgitation may be another mechanism by which AF causes HFpEF (52). Also, depletion of ANP, which may occur in permanent AF, may lead to more vasoconstriction and congestion, and set the stage for incident HFpEF (53).

A mechanism often proposed to explain the development of HF in AF is that of tachycardia or irregularity-induced cardiomyopathy, including hemodynamic changes (shortened diastasis, reduced cardiac output), structural effects (LV eccentric remodeling, subendocardial fibrosis, impaired myocardial perfusion), cellular impact (cytoskeletal alteration, matrix and mitochondrial disruption, abnormal calcium handling), and neurohormonal activation (up-regulation of the renin-angiotensin-aldosterone and natriuretic peptides) (54,55). However, these mechanisms classically pertain to HFrEF, and their contribution to HFpEF remains poorly understood. It is also possible that some cases of so-called HFpEF with AF may be patients in whom LVEF has recovered with adequate heart rate control.

Diagnostic uncertainty

Diagnosing HFpEF in the context of AF is challenging. HF remains a clinical syndrome characterized by the concordance of: 1) clinical symptoms and signs; 2) objective evidence of LV diastolic dysfunction; 3) increased circulating natriuretic peptide levels; and 4) response to therapy (12,56). The first 3 diagnostic components are difficult to establish in the presence of AF because symptoms of HF resemble those of AF, echocardiographic parameters of diastolic dysfunction are more challenging to obtain, and natriuretic peptide levels are elevated in patients

with AF, even in the absence of HF. Although reduced LVEF in AF patients can be diagnosed with different cardiac imaging modalities, identifying HFpEF requires a combination of heterogeneous echocardiographic parameters (57). As a result, there is often clinical reluctance to categorically state the presence of HFpEF in coexisting AF. Furthermore, there is considerable variation in the definition of HFpEF regarding the cutoff of LVEF (2). Although current guidelines recommend LVEF ≥50%, such definitions are arbitrary and may not apply to individual patients. The last of the 4 diagnostic components, response to therapy, seems of potential value, yet is underutilized in HFpEF and AF. Diuretic therapy may provide symptomatic benefit in patients with AF, concomitant HFpEF, and signs of fluid overload (58). Although there are no controlled trials available, improved fluid balance and symptom relief with diuretic therapy, in the absence of any change in heart rate or rhythm, are powerful clinical indicators of the presence of HFpEF in AF patients (**Central Illustration**).

Echocardiography and natriuretic peptides

A number of studies have demonstrated elevated filling pressures in AF, and have validated echocardiographic parameters in AF patients against invasive pulmonary capillary wedge pressure and clinical outcomes. For example, E/e' was significantly associated with filling pressure (5 studies with n = 444; correlation 0.47 to 0.79) (59-63), and independently associated with mortality (64), exercise capacity (65), prior ischemic stroke (66), and quality of life (67). A number of other diastolic indexes also correlate with invasive filling pressure, such as isovolumic relaxation time (IVRT), mitral deceleration time, diastolic flow progression (E/Vp), and pulmonary venous flow measures (68). These results confirm that HFpEF (i.e., the presence of elevated LV filling pressure and HF symptoms) does exist in patients with AF and can be diagnosed, albeit from small observational studies with highly selective inclusion.

The difficulty in making definitive diagnoses of diastolic dysfunction by echocardiography or the presence of HF by elevated levels of natriuretic peptides lies in AF being a known modifier of the relationship between each of these variables and HFpEF. For example, in the case of HFpEF and DproBNP, AF is related to HFpEF and also independently leads to elevation of NT-proBNP, thus potentially distorting the relationship between HFpEF and NT-proBNP. As a result, it remains unclear which NT-proBNP cutoff to use for the diagnosis of HFpEF in the setting of AF, and to what extent NT-proBNP levels respond to treatment (2). Similarly, dilation and dysfunction of the LA, which, in sinus rhythm, is a useful diagnostic criterion for HFpEF (69), may be pre-existing in patients with AF. In most clinical cases, the diagnosis of diastolic dysfunction requires categorizing patients using a range of different parameters (70), not all of which will be abnormal, thus creating clinical uncertainty. These are also critical challenges in designing clinical trials for HFpEF and AF.

Prognosis of concomitant AF and HFpEF

Both prevalent and incident AF are associated with increased mortality in HFpEF (HRs: 1.30 and 2.45, respectively, compared with patients with no AF) (24). Conversely, the presence of HF substantially worsens the prognosis in patients with AF (71,72). However, the type of HF may have different effects on different outcomes. In a meta-analysis of 10 studies, all-cause mortality was significantly higher in patients with HFrEF and AF than in those with HFpEF and AF (risk ratio 1.24, 95% CI: 1.12 to 1.36; $p < 0.001$; n = 45,100), whereas HF hospitalization and incident stroke were similar, regardless of ejection fraction (9). In the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial, stroke rates in HFpEF patients were doubled in those with a history of AF, regardless of whether they were in AF at the time of assessment (73). Sex differences in HFpEF were also noted in I-PRESERVE, with a greater

adverse prognostic effect of AF in women compared with men (74). In observational studies, patients in sinus rhythm with HFrEF had markedly worse symptoms, functional capacity, and quality of life compared to patients with HFpEF, whereas in AF patients, there were no differences between HFrEF and HFpEF (75).

Current and future treatment opportunities

There are no treatments for patients with HFpEF and AF that have been shown to improve prognosis, aside from anticoagulation (26,76). HF therapies that reduce mortality and morbidity in HFrEF, such as angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, and mineralocorticoid-receptor antagonists, do not have the same impact in HFpEF (77-79). The added consequences of AF may also neutralize the mortality benefit of other therapies, such as beta-blockers or digoxin (5,80).

Anticoagulation in AF patients is required when patients have clinical risk factors for stroke or thromboembolism, and current guidelines highlight the risk associated with both HFrEF and HFpEF on the basis of growing evidence that stroke rates are increased in AF patients with either type of HF (9,81,82). Although no trial has specifically randomized AF patients with HFpEF to anticoagulation, subgroup data from the nonvitamin K antagonist oral anticoagulant (NOAC) trials suggest similar efficacy in patients with and without HF (83).

Other treatments of concomitant HFpEF and AF aim to reduce symptoms and improve quality of life (**Central Illustration**). The mainstay of management is therefore to optimize fluid balance, control blood pressure, and avoid ischemia, in addition to managing comorbidities, such as obesity, airway diseases, and diabetes (3). Aggressive risk factor management programs, including weight loss, have reduced AF recurrences and symptoms in AF patients (84-87) and improved cardiorespiratory fitness in HFpEF patients (88). This supports the notion that

adequate treatment of comorbidities and risk factors may improve symptom burden, quality of life, and improve exercise capacity. Rate control of AF in the context of HFpEF is not expected to improve hard endpoints, and any benefit with regard to quality of life, exercise capacity, or cardiac function are yet to be determined, including in older patients, who form the majority of this group (89). Some data suggest reduced symptoms with rate control, although the AF populations assessed were not specifically those with HF or HFpEF (90,91). In elderly patients with severe symptoms related to HFpEF and AF, it seems reasonable to start with rate control to optimize ventricular filling time and prevent symptoms related to paroxysms of rapid AF. Adopting a rhythm control strategy is challenging in patients with HFpEF; often patients are of advancing age and have multiple other comorbidities that may influence the success and risk of complications. Nevertheless, from a small single-center study, catheter ablation in HFpEF was associated with improved diastolic function in patients who maintained sinus rhythm (albeit with multiple procedures and/or antiarrhythmic drugs) (92). Early rhythm control strategies, which are currently under investigation, may increase the beneficial effects on symptom burden, and potentially improve prognosis (93). More advanced AF ablation techniques, including hybrid epicardial and endocardial ablation, offer promise for reducing the AF burden, even in patients with advanced atrial remodeling, such as those with HFpEF.

Emerging medical therapies offer a glimmer of hope (94). In view of potential atrial endocrine failure in HFpEF with AF (discussed earlier) and the utility of neprilysin inhibitors to restore ANP levels, it is noteworthy that the angiotensin receptor-neprilysin inhibitor LCZ696 reduced LA volume in HFpEF in the PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) phase II trial (95). LCZ696 was equally effective in improving outcomes in the presence or absence of AF in the

PARADIGM-HF trial (Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure) in patients with HFrEF (96).

Implantable cardiac devices may also affect the prognosis in patients with HFpEF, with and without AF. Sudden cardiac death accounts for a sizeable proportion of deaths in HFpEF trials (97,98); however, uncertainty remains regarding the true incidence of sustained ventricular tachyarrhythmia and arrhythmic death in the general HFpEF population. Clarifying this uncertainty is of great importance because this may set the stage for implantable defibrillator therapies in HFpEF. The VIP-HF (Ventricular tachyarrhythmia detection by Implantable Loop Recording in Patients with Heart Failure and Preserved Ejection Fraction) registry is currently recruiting patients, and is due to report in late 2018 (99). Whether cardiac resynchronization therapy (CRT) is beneficial in HFpEF with and without AF needs to be determined. Substudies of CRT trials have shown that patients with less severe LV dysfunction (LVEF >35%) appeared to derive clinical and structural benefit from resynchronization (100). However, as mechanical dyssynchrony in HFpEF differs from that seen in classical HFrEF indications (101), the value of CRT in HFpEF patients with AF needs to be explored in future trials.

Knowledge gaps

Despite the increasing understanding of HFpEF and AF separately, there are still important knowledge gaps. Further study is essential to advance our understanding of the pathogenesis, risk, prevention, and treatment of concomitant HFpEF and AF. In **Table 1** we summarize knowledge gaps and potential future research topics, such as defining the global burden of AF in HFpEF and vice versa, identifying genomic and nongenomic risk factors, determining the clinical effect of rate versus rhythm control, and clarifying optimal heart rate targets. To address these questions, we advocate multidisciplinary and translational research

programs capitalizing on experimental studies, observational community-based cohorts, and clinical trials. There are also opportunities for future research in the area of diagnosis, particularly new cardiac imaging techniques, novel clinical indexes, and measures of LA function.

Summary and conclusions

Although HFpEF and AF frequently coexist, there are still numerous unanswered questions about the pathophysiology, symptomatology, diagnosis, and prognosis of both conditions when occurring together. More systematic research is urgently needed to answer these unresolved issues, and to provide treatments that can improve quality of life and reduce adverse clinical outcomes in the rapidly expanding number of patients with HFpEF and AF.

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FIGURE LEGENDS

Central Illustration: Diagnosis and Management of Concomitant HFpEF and AF

*The ratio of mitral peak E velocity to tissue Doppler e': >15 septal and >13 lateral are associated with adverse outcomes in AF patients. Other indexes are also helpful, such as mitral deceleration time, isovolumic relaxation time and pulmonary venous flow. Note that echocardiographic determination of diastolic dysfunction is different in patients with AF due to the lack of mitral inflow A wave, loss of pulmonary venous flow A reversal and different "normal value: ranges compared to sinus rhythm (e.g., diminution of pulmonary venous systolic flow in AF). †NT-proBNP ≥600 pg/ml, as used in the SOCRATES-Preserved study (NCT01951638), or >900 pg/ml, used in the PARAGON-HF trial (NCT01920711). AF = atrial fibrillation; ECG = electrocardiogram; HFpEF = heart failure with preserved ejection fraction; NOAC = nonvitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist oral anticoagulant.

Figure 1: Prevalence of HFpEF in AF

The prevalence of HFpEF in 4 major AF trials. The percentage with left ventricular ejection fraction above 40% or 50% is indicated in the columns, as is the type of AF. AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction.

Figure 2: Prevalence of AF in HFpEF

The prevalence of AF in HFpEF varies in 7 large heart failure trials. Abbreviations as in **Figure 1**.

Figure 3: Pathophysiology and Shared Mechanisms in HFpEF and AF.

Common mechanisms involved in HFpEF, AF, and the combination of these conditions. ANP = atrial natriuretic peptide; LV = left ventricular; RAAS = renin-angiotensin-aldosterone system.

Other abbreviations as in **Figure 1**.

Table 1. Knowledge Gaps and Areas Essential for Advancing Understanding of the Pathogenesis, Prevention, and Treatment of Concomitant HFpEF and AF

Research Domain	Important Knowledge Gaps	Areas of Potential Discovery and Scientific Advancement
Epidemiology	Incidence and prevalence of HFpEF in the setting of AF. Global burden of HFpEF and AF.	Identification of the clinical, subclinical, and genomic factors underlying variability in AF and HFpEF, life course, and complications in diverse racial groups, populations and regions. Discovery of strategies to prevent AF onset and progression in the setting of HFpEF, and vice versa.
Noninvasive imaging	Diagnosis of HFpEF in the setting of AF.	Novel methods for assessing diastolic function and, in particular, for quantifying LA function are within reach. Measuring LA volume using 3-dimensional echocardiography, quantifying LA function with speckle-based strain and velocity vector imaging (102).
Natriuretic peptides	Optimal cutoff values for diagnosis of HFpEF in	Clinical classification of patients to enable stratified therapy and a more

	patients with AF.	personalized approach.
Clinical cardiology	Treatment of AF in the setting of HFpEF. Treatment of HFpEF in the setting of AF.	Investigation of rate and rhythm control in AF and HFpEF, and improvement in symptom burden and prognosis. Confirmation that the benefits of physical activity and lifestyle modification seen in HFpEF (88) and AF (87) also occur in patients with both conditions. Development of novel therapeutic agents in patients with HFpEF that are also beneficial in those with concomitant AF. Further data on patient care managed by hemodynamic monitoring (103) Investigation of device therapies in AF and HFpEF.
Systems biology	Relations between clinical risk factors, genetics, and environment.	Integration across multiple disciplines (basic science, epidemiological, clinical, bioinformatics) will accelerate our understanding of complex pathways underlying AF and HFpEF, and develop opportunities for prevention and treatment.

AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction; LA = left atrium/atrial

Diagnosis of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF)

	HFpEF	AF	Combined
Symptoms			
Breathlessness	+	+	++
Fatigue	+	+	++
Orthopnea	+	–	+
Nocturnal dyspnea	+	–	+
Signs			
Increased venous pressure	+	–	+
Rales/third heart sound	+	–	+
Irregular pulse	–	+	+
Investigations			
AF on ECG or device	–	+	+
Left atrial enlargement	+	+	++
Increased E/e' ratio on echo*	+	–	+
Increased natriuretic peptides†	+	+	++
Clinical response to diuretics	+	–	+

Treatment recommendations for AF and HFpEF

Prognostic

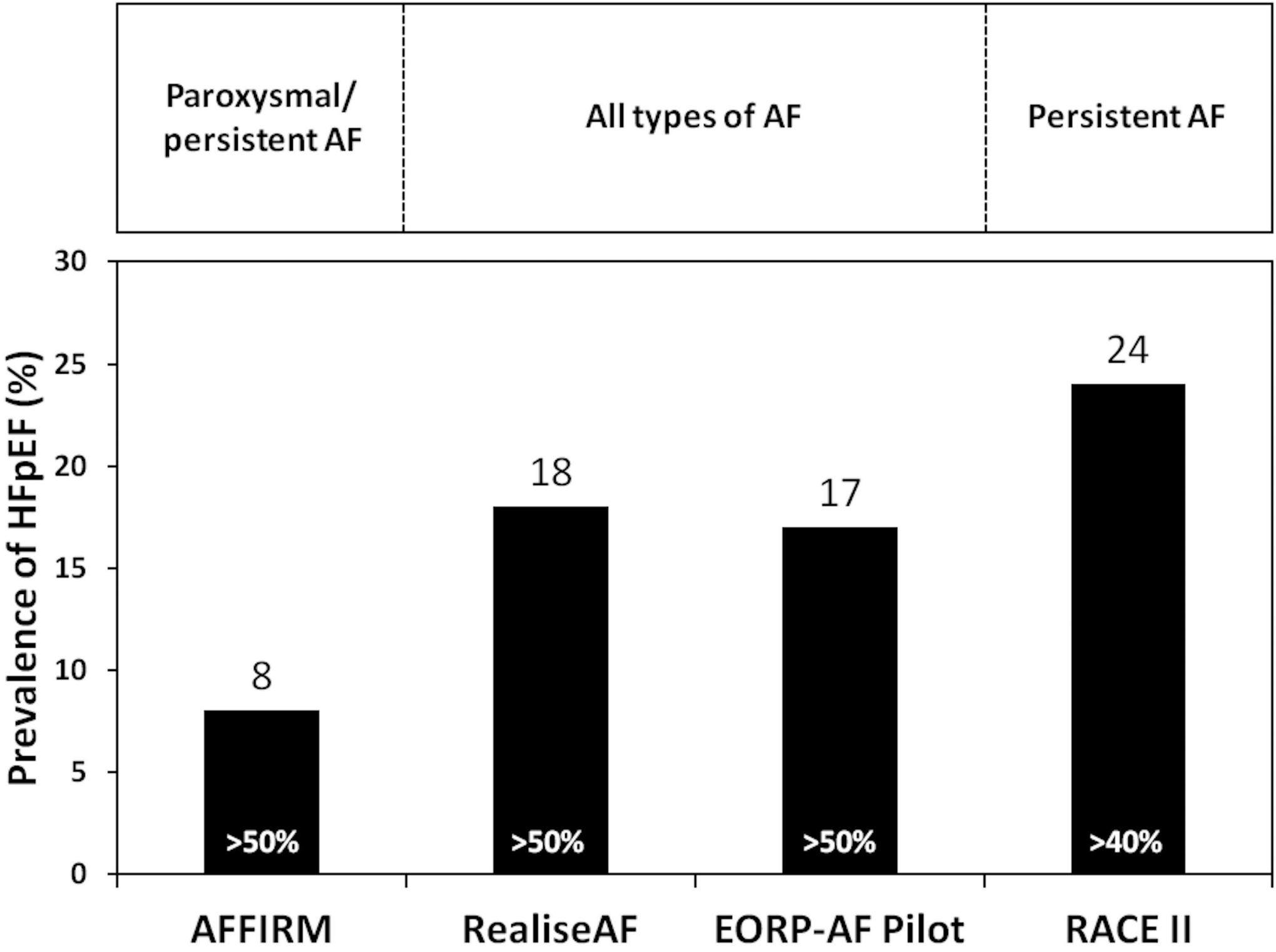
Anticoagulation with NOACs or VKA (all patients ≥65 years or other risk factors)

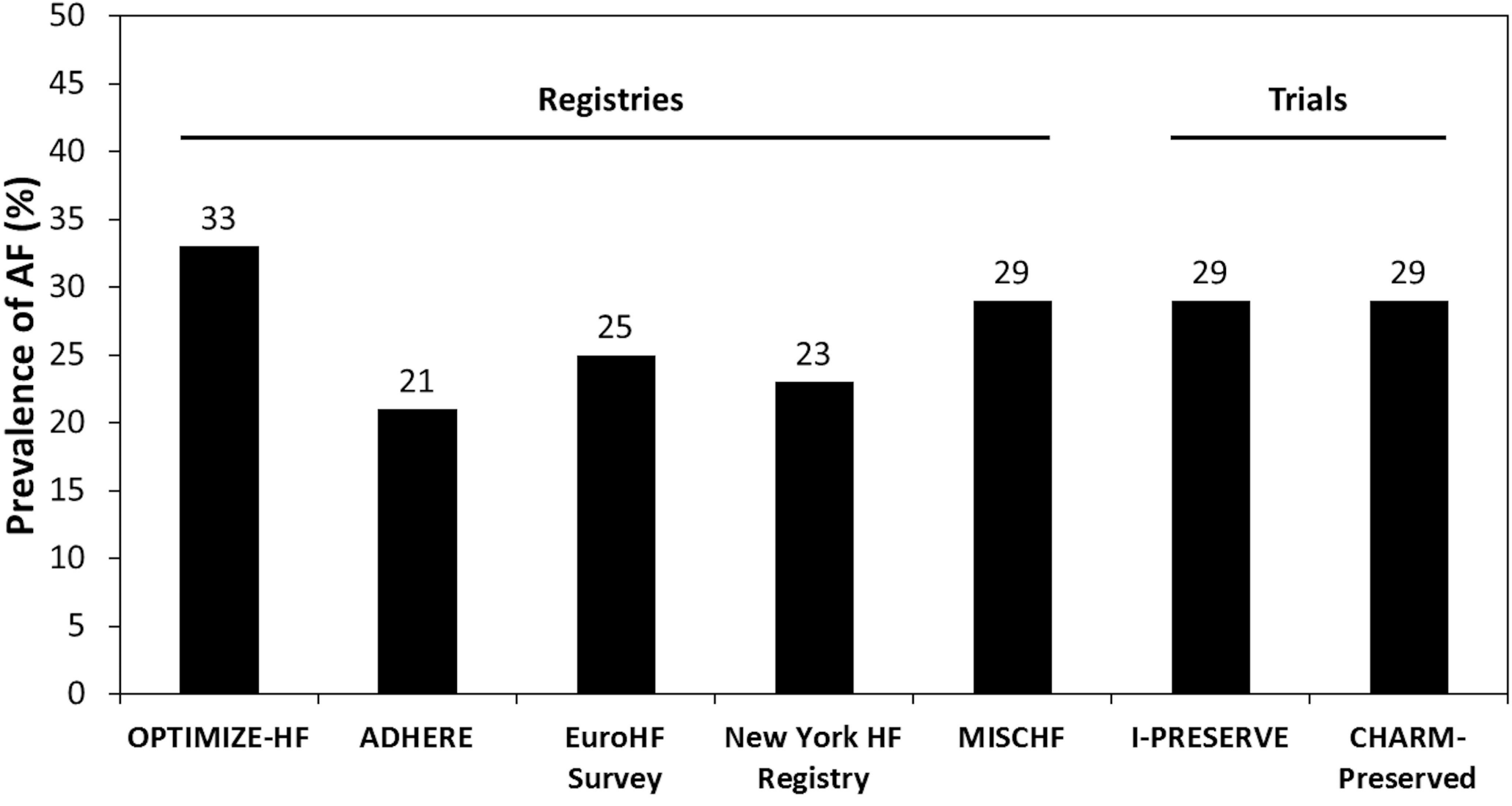
Disease modifying

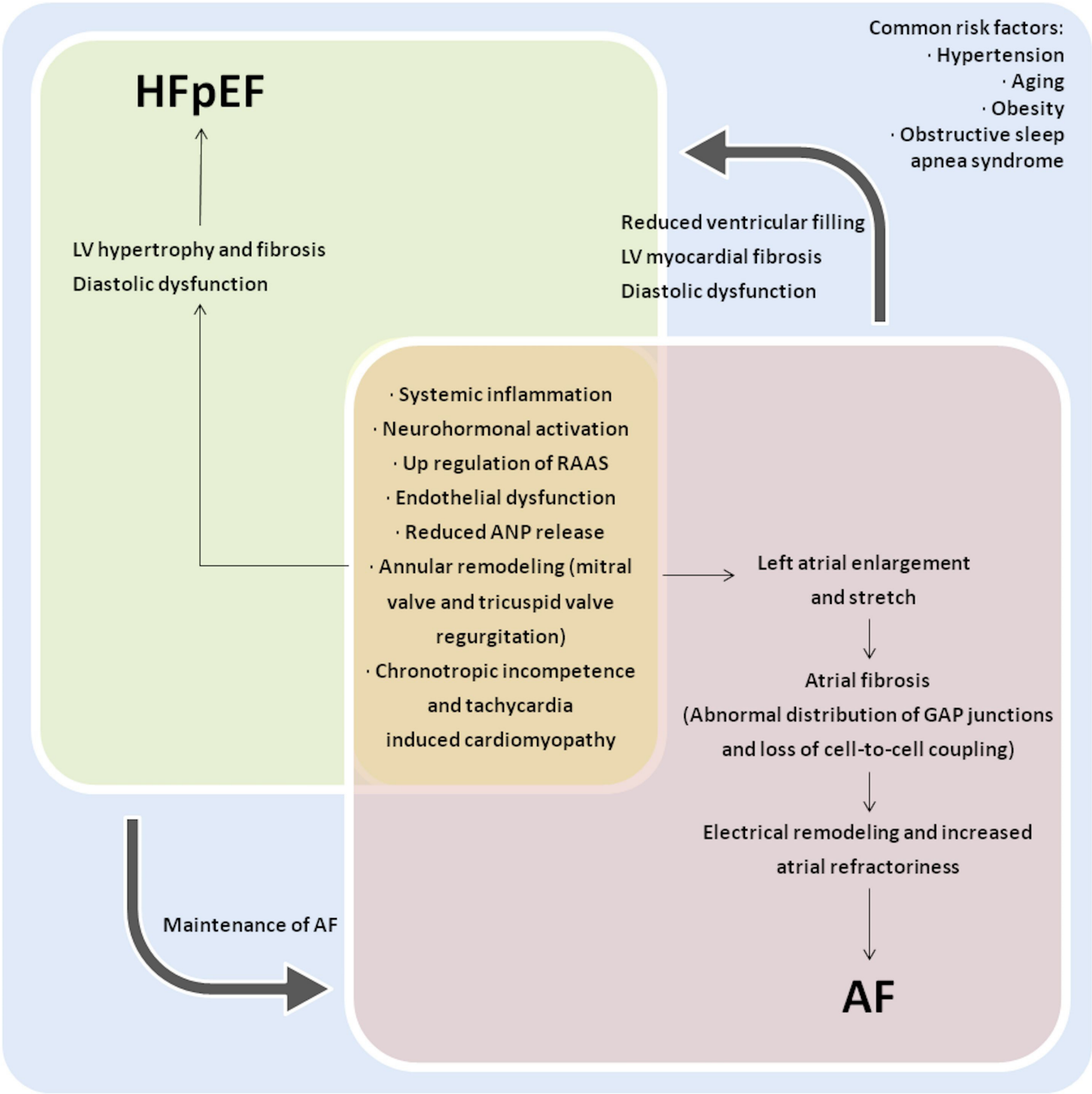
- Anti-hypertensive therapy
- Treatment of myocardial ischemia
- Management of associated comorbidities

Symptomatic therapy

- Diuretics
- Heart rate control (resting <110 bpm; lower if ongoing symptoms)
- AF rhythm control


Paroxysmal/ persistent AF
All types of AF
Persistent AF
Prevalence of HFpEF (%)
30
25
20
15
10
5
0
8
18
17
24
>50%
>50%
>50%
>40%
AFFIRM
RealiseAF
EORP-AF Pilot
RACE II


Prevalence of AF (%)
50
45
40
35
30
25
20
15
10
5
0
Registries
Trials
33
21
25
23
29
29
29
OPTIMIZE-HF
ADHERE
EuroHF Survey
New York HF Registry
MISCHF
I-PRESERVE
CHARM-Preserved


Common risk factors:
· Hypertension
· Aging
· Obesity
· Obstructive sleep apnea syndrome
HFpEF
LV hypertrophy and fibrosis
Diastolic dysfunction
Reduced ventricular filling
LV myocardial fibrosis
Diastolic dysfunction
· Systemic inflammation
· Neurohormonal activation
· Up regulation of RAAS
· Endothelial dysfunction
· Reduced ANP release
· Annular remodeling (mitral valve and tricuspid valve regurgitation)
· Chronotropic incompetence and tachycardia induced cardiomyopathy
Left atrial enlargement and stretch
Atrial fibrosis
(Abnormal distribution of GAP junctions and loss of cell-to-cell coupling)
Electrical remodeling and increased atrial refractoriness
AF
Maintenance of AF

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Article entitled: Vicious Twins - Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

Manuscript number: JACC080316-3226N

Corresponding Author: Dr. Rienstra

Corresponding author's printed name: Isabelle C Van Gelder

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